An Integrated System For Treating And Monitoring Sickle Cell Disease

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Abstract

Sickle Cell Disease (SCD) is a genetic disorder that affects approximately 100,000 Americans of whom are of Black and Hispanic decent. SCD is caused by a mutated gene that changes the shape of hemoglobin in red blood cells and causes them to become sickle shaped. When sickled shaped cells clog the blood vessels it causes enormous pain, leading to acute chest syndrome, strokes, and severe anemia. Our team is proposing a three part integrated approach to treating and monitoring SCD. The first approach involves transplanting hematopoietic stem cells that carry the gene (HbA) for normal hemoglobin directly into a fetus. Our team's second approach involves reactivating the fetal hemoglobin gene in adults suffering from SCD. The third component is a medical tricorder that detects and measures SCD biomarkers. Data from the tricorder will be wirelessly transmitted to a doctor/caregiver to alert them of changes in a SCD patient's condition.

Present Technology

Our Exploravision project, “An Integrated System for Treating and Monitoring Sickle Cell Disease," is a topic that is very important to our team since two of the members have been diagnosed with Sickle Cell Trait (SCT). Approximately 2 million Americans have SCT including one in twelve African Americans. Individuals with SCT carry a single abnormal gene for sickle cell disease and can pass the gene along to their children. If however an individual inherits two abnormal genes, they will be diagnosed with Sickle Cell Disease (SCD), a life threatening condition. Approximately 100,000 people in America live with SCD, and although it affects people of many different ethnicities, it mainly occurs in Blacks and Hispanics.

SCD is caused by a mutated version of the gene that changes the shape of the hemoglobin molecule and makes it clump together. Hemoglobin is the protein molecule found in red blood cells, which carries oxygen throughout the body. When red blood cells carry mutated hemoglobin the cells are deprived of oxygen causing them to change from a doughnut/ disc shape to a sickle like shape. Deformed red blood cells will become stiff and clog blood vessels depriving the body’s tissues and organs of the oxygen they need to function. When the sickle shaped cells clog the blood vessels it causes an enormous amount of pain, and can lead to acute chest syndrome, strokes and severe anemia.

Antibiotics prescribed over a long period of time are one of the technologies used to treat children and teens diagnosed with SCD. Children and teens with SCD are prone to serious infections and are treated with penicillin beginning at two months of age, and continue until they are at least five years old. Taking an antibiotic can help prevent infections such as pneumonia, and septicemia. Septicemia is a deadly blood infection that frequently occurs in children and

teens suffering from the disease. Taking antibiotics over a long period of time however, increases the risk that infections can become resistant to the antibiotics.

People with SCD have a high risk of suffering from a stroke, or severe anemia, and to lower the risk of these complications blood transfusions are often administered to the patient. Blood transfusions are a process in which an individual donates healthy blood cells to the person with SCD. Blood transfusions lower the amount of hemoglobin S (HbS), which is the abnormal form of hemoglobin, and increases the normal form of hemoglobin, which is hemoglobin A (HbA). Transfusions also increase the number of red blood cells in the body, which means the supply of oxygen is increased. There is however a major limitation to a patient receiving repeated blood transfusions. Iron overload (Hemochromatosis) is a complication that can cause liver, heart, and pancreatic disease.

Hydroxyurea is another drug that is used for treating SCD. This drug increases the amount of fetal hemoglobin (HbF) in the body and raises the total hemoglobin concentration. HbF is the hemoglobin that transports oxygen through a developing fetus in the last seven months of pregnancy. HbF protects babies born with SCD for six months; however, by the time the baby is one year of age HbF is replaced by the deformed sickled cells. Hydroxyurea keeps the hemoglobin levels raised in children and adults taking the medication.

Bone marrow transplant (BMT) is another technology that is currently used to treat people with SCD. Red blood cells are produced from stem cells that are found in bone marrow. A bone marrow transplant replaces stem cells in the bone marrow that produces HbS with stem cells that produce HbA. Before receiving the BMT the patient must undergo chemotherapy that weakens and destroys the patient's bone marrow stem cells, and infection fighting system. Once

the chemotherapy is completed donated bone marrow cells are transfused into the SCD patient. The donated bone marrow stem cells then begin to produce normal red blood cells and restore the immune system. Although bone marrow transplants are considered a cure for SCD there are major limitations. If the transplant is unsuccessful the patient is susceptible to serious infection. Chemotherapy also leads to death in 5 to 10% of the cases. In addition BMT's are very expensive, and therefore are out of the question for many struggling families.

History

SCD is known as "The Forgotten Disease," for a very good reason. Although SCD is the most commonly inherited blood disease, there has been a major difference between research funding for SCD and other inherited diseases. For example, "in 2003 the National Institute of Health (NIH) paid almost four times more money for Cystic Fibrosis than SCD". Further more, in 2003 the Sickle Cell Disease Association of America's total revenue was $498,577 compared to the Cystic Fibrosis Foundation revenue of $152 million. Therefore, the history section of this paper is very limited, but includes the following:

In 1910, Dr. James B. Herrick provides the first description of SCD.

In 1940, Sherman discovers that the sickling of red blood cells is caused by a change in hemoglobin.

In 1949, Linus Pauling showed that sickle cell hemoglobin differed in structure from normal hemoglobin and that the cause of the disease was linked to a change in protein structure.

In 1984, a bone marrow transplant produced the first cure for a child with SCD. However bone marrow transplants were not used on a regular basis until much later.

In 1995, Hydroxyurea was the first drug to be used to reduce painful complications of SCD.

In 1997, blood transfusions were given to children to decrease the risk of stroke.

In 2009, a study showed that stem cell transplants reverse sickle cell disease in adults.

Future Technology

After meeting with Dr. Marjorie DeJoie, Medical Director of the Philadelphia Chapter of the Sickle Cell Disease Association of America; Stanley A. Simpkins Executive Director of the Center; Zemoria Brandon, social worker at the Center, and interviewing Dr. Kim Smith-Whitley, Medical Director of the Sickle Cell Center of the Children's Hospital of Philadelphia (CHOP), our team's future technology proposal changed drastically. Our first approach was to propose a single cure for SCD; however after our discussion with the experts we realized there must be multiple approaches to curing and treating SCD. Therefore, our team's future technology proposal will include treatments for fetuses and adults carrying the gene for SCD, and a medical tricorder to monitor their health after the treatments.

Since 2004, all newborn babies in the United States have been tested for SCT and SCD, which mean that future adult generations will know if they carry SCT, or have SCD. Identifying the disease in the parents allows doctors to know which fetuses have a higher risk of carrying the gene or having the disease. In the future, if it is determined that a fetus has SCD, doctors will be able to treat the baby before it is born.

Our team's proposal is to transplant Hematopoietic stem cells (HSCs), which carry the gene for normal HbA, directly into the fetus. HSCs can form every type of cell in the blood such as red blood cells, white blood cells and platelets, and can be found in bone marrow, peripheral blood (blood in veins) and umbilical cord blood.

Umbilical cord blood and placentas are rich in HSCs. Transplanting cord blood to treat SCD patients is a better alternative than bone marrow transplants for several reasons. HSCs are easier to collect than bone marrow, the procedure is less likely to cause immune system rejection, and HSCs can easily be frozen and stored until they are needed.

Our team is envisioning that HSCs from cord blood will be delivered directly into the umbilical vein or artery of a fetus diagnosed with SCD. Once a mother's abdomen has been thoroughly sterilized an image will be taken to determine the position of the placenta and fetus. In order to temporality stop fetal movement, medicine may be given. A needle will then be guided through the mother's abdomen and into the fetus's umbilical cord vein or artery using ultrasound. The HSCs would then be transplanted through the umbilical cord and into the fetus's circulatory system, and then travel into the bone marrow.

Recent research studies have discovered that the fetal immune system and the adult immune system come from completely different sets of stem cells. This discovery has influenced our future technology design. Scientists have found that in the first two trimesters " the job of the fetal immune system it is to teach the fetus to be tolerant of everything it sees, including its mother and its own organs. After birth, a new immune system arises from a different stem cell that instead has the job of fighting everything foreign." Therefore, our team is

proposing that the transplanting of the HSC's should occur in the first or second trimester of pregnancy.

After completing research on transplanting HSC's into fetuses, our team focused attention on a future technology for adults with SCD. Scientists have known for quite awhile that fetal hemoglobin is immune to the genetic defect of SCD, and our proposal is based on two very recent scientific studies that have shown fetal hemoglobin can be reactivated in adults (Orkin, 2011 & CHOP, 2014). There are a number of factors in blood cells that turn off fetal hemoglobin. One of the primary factors is BCL11A, a protein that binds to DNA and turns off fetal hemoglobin. Our team is envisioning silencing the BCL11A protein, which will reactivate the fetal hemoglobin. Another approach to reactivating fetal hemoglobin will be to force the chromosomes into looped structures that will activate genes that regulate hemoglobin. Looping the chromosomes brings DNA at specific sites in contact with each other and will reactive fetal hemoglobin.

To ensure that patients who received the treatments listed above remain free of SCD complications, they will need to be closely monitored, and therefore our team is proposing a medical tricorder. This tricorder will detect biomarkers for SCD; a biomarker is "a measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection or environmental exposure."

One very important biomarker for monitoring SCD is Nitric Oxide (NO). Our team learned that as the levels of NO decrease, the pain crises for SCD patients increase. Nitric Oxide is a signaling molecule that directs the arteries to expand when released from the red blood cells, and if NO levels are low the arterial walls don't expand which causes pain. When the sickle

shaped red blood cells attempt passing through the arterial walls they constrict causing a lack of oxygen to the tissues.

Another vital biomarker for SCD is monitoring the blood flow rate. When the sickle shaped blood cells clump together they clog the blood vessels causing an obstruction, which decreases the rate of blood flow depriving the body tissues of oxygen, and also causing severe pain.

Two additional biomarkers that the tricorder will have to measure are high blood pressure and red blood cell count (RBC). High blood pressure increases the risk of having a stroke and about thirty-one percent of children with SCD have suffered from silent strokes. In a silent stroke, there are no symptoms such as excruciating headaches, one side paralysis of the face or body, and loss of speech or vision, but they do cause brain damage. Red blood cell count also has to be monitored because sickle cells have a life span of about ten to twenty days and normal red blood cells last up to 120 days. This means that the organs are being deprived of oxygen and can lead to severe anemia.

The tricorder we are envisioning is a non-invasive wearable device that will measure multiple biomarkers and transmit data to a caregiver or doctor. Our team's device will be worn on the wrist and will use Doppler ultrasonography, which changes sound waves to an image that can be viewed, to measure the direction, velocity and turbulence of the blood flow of the SCD patient.

Also built into the tricorder will be a sensor to monitor blood pressure. The sensor will record the pulse wave, which is the pressure that radiates through the arteries when the left ventricle contracts. Using "computerized mathematical modeling of the pulse wave", blood

pressure close to the heart and brain can be accurately read. Our team's technology will be especially important to SCD patients because it will measure blood pressure close to the brain, to detect and prevent silent strokes.

A pulse oximeter will also be built into the medical tricorder and will measure oxygen levels of the SCD patient. The pulse oximeter will compare how much red light and infra red light the SCD patient's blood absorbs. If hemoglobin is attached to oxygen, then blood will be bright red as compared to blood with less oxygen, which will be a dark red. The bright red oxygenated blood will absorb infrared light while the darker red deoxygenated blood will absorb red light.

One of the most important biomarkers for our medical tricorder is nitric oxide (NO). Our team's proposal for measuring NO is based on a study from Princeton University (Wysocki, 2014). The tricorder will use optical spectroscopy to measure NO in the SCD patient's breath. In order for the optical spectroscopy to take place a laser, a gas cell between two polarizer's, and a photo detector will need to be embedded inside of the tricorder. The SCD patient will breathe into a small tube that is attached to the side of the tricorder device. Once finished the tube will be placed back into the groove of the tricorder.

The tricorder monitoring data will be wirelessly transmitted to a doctor and to a caregiver of the patient. The data that is received will be used to ensure that treatment for SCD is functioning properly, and to determine whether or not the patient's condition has evolved. For example, if a child's systolic blood pressure goes above 113, the tricorder will alert the doctor and caregiver, because there is a four-fold risk of a child having a silent stroke with a systolic blood pressure above 113.

Breakthroughs

An ample amount of research needs to be conducted in order to ensure that the hematopoietic stem cells that are being transplanted into the fetus transform into normal red blood cells. If not, the hematopoietic stem cells could possibly form into hair cells, skin cells, tumor cells, or even sickled cells. A second major breakthrough will need to be the development of micro/nanoscale-structured materials that will be built into the tricorder. Currently, things like lasers that will be needed in our tricorder are too big to be placed inside of our team's monitoring device.

Another important breakthrough will be raising sickle cell awareness throughout Black and Hispanic communities. Our proposed technology won't matter if no one is aware of SCD and proposed treatments. Awareness will need to be raised through health education, social media, lobbying, and intense social activism. Successful health campaigns could be studied as ways to increase awareness about SCD. For instance, the anti-smoking campaign has been very successful and could be used as a model for a SCD campaign.

Design Process

Our teams design process drastically changed over time. The first major change came after we visited the Philadelphia Chapter of the Sickle Cell Disease Association of America. We figured there would be a single cure for SCD in the future however, after the visit we learned that there would need to be multiple treatments for SCD. Our first proposed technology was going to be a large SCD scanner that would be stationary and located in a doctors office, this idea was rejected because its not practical for a SCD patient to continuously visit a doctors office for

monitoring. Initially our team envisioned a hand held device for monitoring SCD patients. This idea was changed in favor of a wearable device because our team thought it would be more convenient. A child with SCD isn't going to be responsible with a portable device, whereas a wearable device doesn't have to be placed anywhere other than the wrist.

Consequences

Negative: Every medical procedure has risks including stem cell and gene therapy. A feasible risk for both treatments may be the development of cancers or tumors. Once an individuals DNA is changed it can lead to unintended consequences. Also unwanted immune system reactions, can cause inflammation, and in severe cases organ failure. As for our proposed tricorder, a possible negative consequence is that the wireless transmission of medical data could get into the hands of the wrong people, and be used to discriminate against the patient with SCD. The National Department of Homeland Security stated, "Failure to implement a robust security program will impact the organizations ability to protect patients and their medical information from intentional and unintentional loss or damage."

Positive: The positive consequences for our proposed technology far outweigh the negative ones. Our proposed technology will relieve SCD patients from their daily debilitating suffering, help them to live a normal life, and greatly reduce costs of their medical treatments. Once our proposed technologies are available they are sure to pave the way for treating other inherited blood disorders.

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In Person Interviews

Dr. Marjorie Dejoe, medical director of the Philadelphia chapter of the Sickle Cell Disease Association of America

Stanley A. Simpsons Execcutive Director of the Center of Philadelphia Chapter of the Sickle Cell Disease Association of America

Zemoria Brandon Administrator/ Social worker of the Philadelphia Chapter of the Sickle Cell Disease Association of America

Phone Interview

Dr. Kim- Whitley, Medical Director of the Sickle Cell Center of the Children's Hospital of Phildelphia

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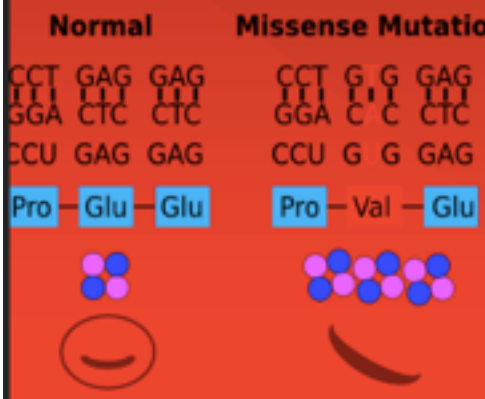
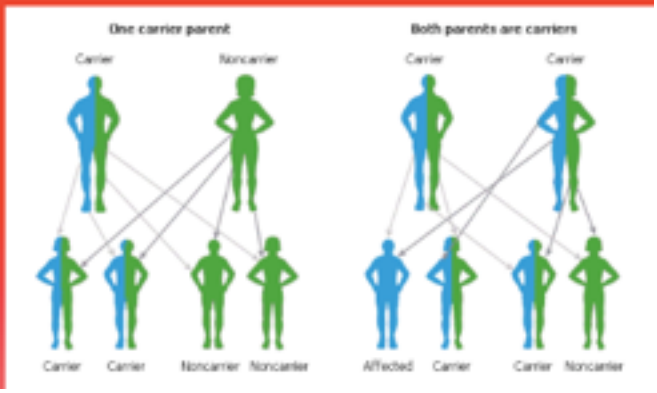
Genetics of Sickle Cell Disease



Sickle Cell Disease(SCD) is caused by a mutated version of the gene that changes the shape of the hemoglobin molecule and makes it clump together. When the sickle shaped cells clog the blood vessels it causes an enormous amount of pain and can lead to acute chest syndrome, strokes, and anemia.

When an individual inherits a mutated gene from each parent there is a 25% chance of having Sickle Cell Disease, a 50% chance of Sickle Cell Trait, and 25% chance of not being affected.



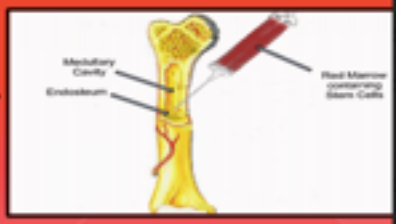
Sickle Cell Present Technology

Penicillin is a drug that helps prevent deadly infections such as pneumonia and septicemia.

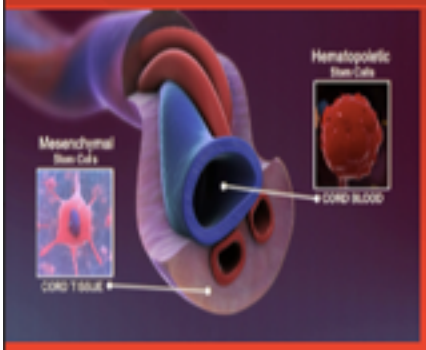
Blood transfusions lower the amount of sickle cell hemoglobin (HbS)and increase the amount of norm hemoglobin(HbA).

Hydroxyurea is a drug that reactivates the fetal hemoglobin in an SCD patient.

Bone Marrow Transplants replace stem cells in the bone marrow that produce HbS with stem cell that produce HbA.

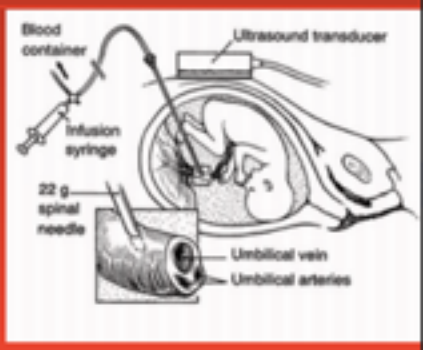


Future Technology Treatments

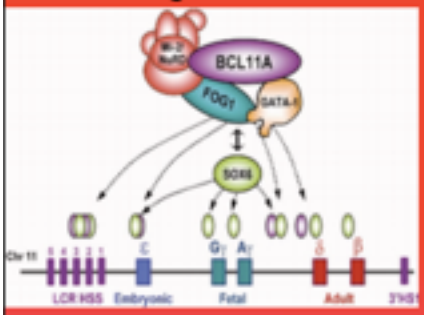


Stem Cell Therapy

Umbilical cord blood is rich in Hematopoietic Stem Cells(HSC's), which carry the gene for normal HbA. The HSC's will be transplanted directly into a fetus to replace the sickle stem cells that have the SCD gene.



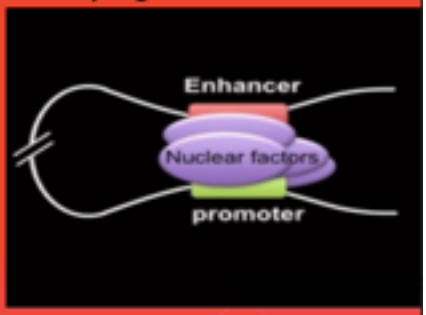
Silencing BCL11A

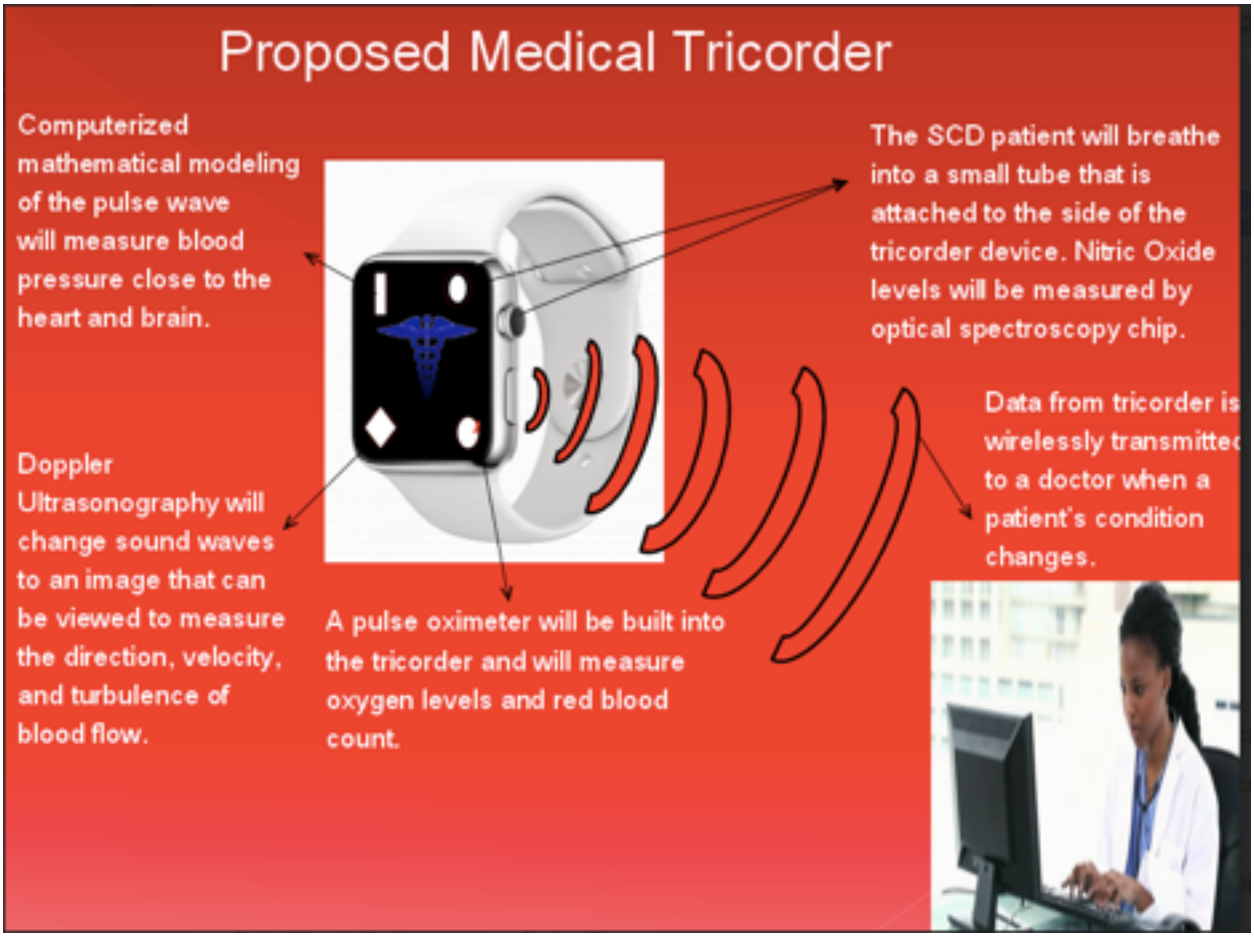


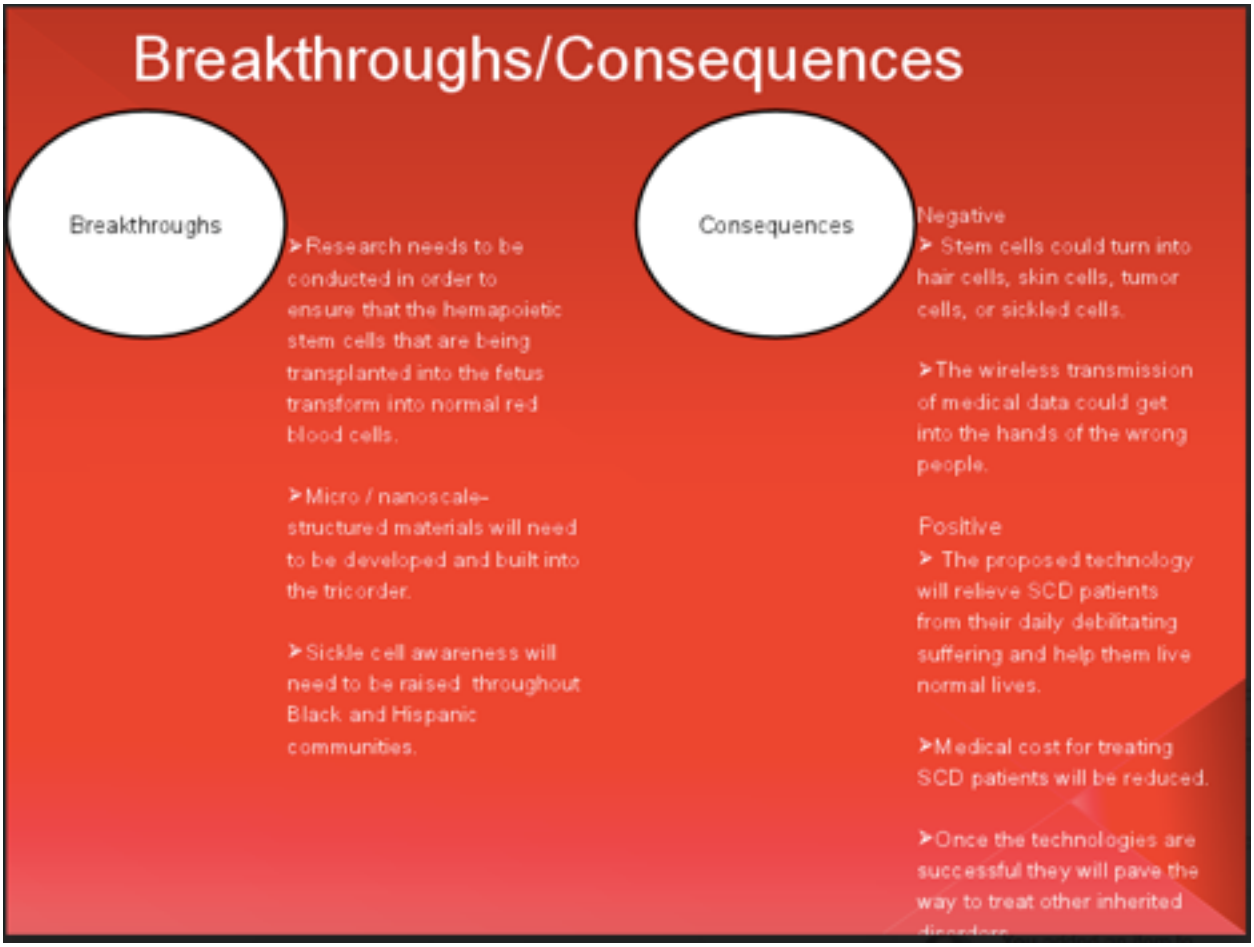
Gene Therapy

One of the factors in blood cells that turn off HbF is BCL11A. When BCL11A binds to DNA it turns off HbF. Silencing the BCL11A protein will reactivate HbF. Forcing chromosomes into loops brings DNA at specific sites in contact with each other and reactivates HbF.

Looping Chromosomes




Proposed Medical Tricorder
Computerized mathematical modeling of the pulse wave will measure blood pressure close to the heart and brain.
The SCD patient will breathe into a small tube that is attached to the side of the tricorder device. Nitric Oxide levels will be measured by optical spectroscopy chip.
Data from tricorder is wirelessly transmitted to a doctor when a patient's condition changes.
Doppler Ultrasonography will change sound waves to an image that can be viewed to measure the direction, velocity, and turbulence of blood flow.
A pulse oximeter will be built into the tricorder and will measure oxygen levels and red blood count.


Breakthroughs/Consequences
Breakthroughs
➢Research needs to be conducted in order to ensure that the hemapoietic stem cells that are being transplanted into the fetus transform into normal red blood cells.
➢Micro / nanoscale-structured materials will need to be developed and built into the tricorder.
➢Sickle cell awareness will need to be raised throughout Black and Hispanic communities.
Consequences
Negative
➢ Stem cells could turn into hair cells, skin cells, tumor cells, or sickled cells.
➢The wireless transmission of medical data could get into the hands of the wrong people.
Positive
➢ The proposed technology will relieve SCD patients from their daily debilitating suffering and help them live normal lives.
➢Medical cost for treating SCD patients will be reduced.
➢Once the technologies are successful they will pave the way to treat other inherited